Differences in Dose Scheduling as a Factor in the Etiology of Anthracycline-Induced Cardiotoxicity in Ewing Sarcoma Patients

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Clinical observation suggested a high prevelance of cardiac morbidity and mortality in children with Ewing sarcoma (ES) treated at B.C.'s Children's Hospital. We therefore compared 30 patients treated for Ewing sarcoma between 1978 and 1991 with 26 soft tissue sarcoma (STS) patients treated with similar chemotherapy over the same period of time.

All patients were evaluated for cardiac function using echocardiography. Shortening fraction (SF) and left ventricular mass index (Massl) were compared before and after treatment. The role of chest irradiation, dose concentration (DC) of adriamycin (AD), total mean doses of AD, cyclophosphamide (CY) and actinomycin (AC) were analysed.

SF for patients with ES and STS postchemotherapy was significantly lower ($P \ll .001$ and $P = 0.0004$, respectively) than pretreatment values. Postchemotherapy SF for ES was lower than STS ($P = 0.0097$). Massl for each group did not change significantly. Six of the ES patients had postchemotherapy SF of <0.20, with three in congestive failure, two cardiac deaths and one heart transplant. One additional ES patient had sick sinus syndrome and needed a pacemaker. Among the STS patients only one had SF $< .20$ and none were symptomatic. There were no significant differences in the mean AD, CY and AC doses for ES versus STS. The difference in the DC of AD for ES (mean 744) compared to STS (mean = 362) was significant ($P = < 0.001$). Regression analysis indicated a trend for decreasing SF with increasing DC ($P = 0.017$). Chest irradiation did not appear to increase the likelihood of cardiotoxicity.

ES patients had a higher prevalence of cardiac dysfunction compared to STS. Studies are required to evaluate the importance of the components of DC, i.e., size of the individual dose and frequency of administration of AD, and to look at other possible factors in the causation of cardiomyopathy in ES.

Key words: Anthracyclines, cardiomyopathy, Ewing's sarcoma

INTRODUCTION

Advances in chemotherapy for childhood malignancies have resulted in improved long-term survival, but at the cost of adverse long-term effects. Adriamycin (AD) and the related anthracyclines have a significant role in cancer therapy because of their efficacy in the treatment of hematologic and other solid tumors [1,2] but can produce irreversible and life-threatening cardiotoxicity. Factors thought to be associated with increased risk of AD-related cardiotoxicity include total dose [3–8], chest irradiation [9–12] and cyclophosphamide (CY) [13–16]. Even though there are several reports describing anthracycline cardiotoxicity in childhood, there are scant data on anthracycline cardiotoxicity relative to individual malignancies. There have been recent reports of late cardiac effects of AD therapy in patients with acute lymphoblastic leukaemia of childhood [17,18]. At our institution, long-term follow-up of treated Ewing Sarcoma (ES) patients suggested a high prevalence of cardiac morbidity and mortality. We performed a retrospective analysis comparing the chemotherapeutic regimen, clinical outcome and cardiac function in treated ES patients versus soft tissue sarcoma (STS) from 1978 to 1991, as these patients received similar chemotherapy.

MATERIALS AND METHODS

Patient records from 1978 to 1991 with ES who had completed their chemotherapy at B.C. Children's hospital were reviewed. There were a total of 35 ES patients, of whom five were excluded because of insufficient prechemotherapy data, three patients did not have prechemotherapy echocardiographic assessment, one patient was lost to follow-up, and another patient died of pulmonary embolism following surgery and one course of chemotherapy. There was no cardiac toxicity in these patients.

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Received November 7, 1994; accepted February 22, 1996.

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This work was presented in part at the American Society of Pediatric Hematology and Oncology meeting in Chicago, 1992.

TABLE I. Patient Characteristics

	Ewing sarcoma	Soft tissue sarcoma[a]
Number of patients	30	26
Sex	M = 17, F = 13[b]	M = 16, F = 10
Mean age at diagnosis (yrs)	11.19*	4.38*
Median	11.93	3.91
S.D.	3.50	3.55

[a]Rhabdomyosarcoma, 18; malignant fibrohistiocytoma, 3; leiomyosarcoma, 1; spindle cell sarcoma, 1; neurofibrosarcoma, 1; sarcoma-ethmoid sinus, 1; undifferentiated epidural sarcoma, 1.
[b]F, female; M, male.
*$P = <0.001$.

TABLE II. Drug Combinations for Both Groups

Drug combinations	Number of patients
Adriamycin/cyclophosphamide/actinomycin	41 (ES:25; STS:16)[a]
Adriamycin/cyclophosphamide	9 (ES:5; STS:4)
Adriamycin/actinomycin	02 (STS)
Cyclophosphamide/actinomycin	04 (STS)

[a]ES, Ewing sarcoma; STS, soft tissue sarcoma.

TABLE III. Chemotherapeutic Agents and Dose Relationship Between ES and STS Groups

	ES	STS
Adriamycin (mg/m^2)		
Mean	381.7	334
Median	375	339
S.D.	55	110
n	30	22
$P = 0.07$		
Actinomycin (mg/kg)		
Mean	0.34	1
Median	0.33	0.7
S.D.	0.2	1.3
n	25	24
$P = 0.02$		
Cyclophosphamide (g/m^2)		
Mean	13.9	10.4
Median	14	10.2
S.D.	5	6
n	30	24
$P = 0.02$		

Twenty-six patients with STS treated with similar chemotherapeutic agents over the same time period were selected as controls. Table I shows their clinical data.

The patients had been treated according to the specific treatment protocols in use for the given tumour at the time of diagnosis. Twenty-four patients with ES were treated according to the Intergroup Ewing's sarcoma II regimen A (AD 75 mg/m^2 every 6 weeks) [19]. Five patients were treated using AD 75 mg/m^2 every 3 weeks, and one received AD 60 mg/m^2 every 10 weeks. The STS patients were treated on various regimens according to the Intergroup Rhabdomyosarcoma Study III [20]. Most of these patients received AD at 30 mg/m^2 daily for 2 days every 8 weeks. There were four patients who did not receive any AD (Table II). Since both the size of the individual dose and the frequency of administration were different, the dose concentration for AD was calculated incorporating both factors as variables. Thus, for the purpose of the study, dose concentration (DC) was defined as drug administered per unit time (mg/m^2/day) $\times$ size of the individual dose, i.e.,

$$\text{D.C.} = \frac{\text{D} \times \text{d}}{\text{T}}$$

where D = total cumulative dose of AD in mg/m^2, d = size of the individual dose in mg/m^2, and T = average time interval between doses of AD in days.

The DC was compared for both groups and its correlation to SF. The effect of chest irradiation on SF was also analyzed. Total cumulative doses of AD, cyclophosphamide (CY), and actiomycin (AC) were obtained and compared between groups (Table III).

All patients had baseline and serial standard M mode echocardiography and have been off therapy at least 6 months before the last echocardiographic measurement. The baseline and last M mode echocardiographic measurements were used for analysis. The duration of post-chemotherapy echocardiographic assessment varied from 1 year to 8.76 years (S.D. 2.52 years). Echocardiographic measurements included left ventricular diameter and posterior wall thickness during systole and diastole. Shortening fraction (SF) and Massl to Body Surface Area were calculated [21]. A SF of 0.28 to 0.40 was defined as normal, mild echocardiographic cardiomyopathy as SF 0.20 to 0.27, moderate to severe cardiomyopathy as SF < 0.20. Adverse clinical outcome was defined by congestive cardiac failure or death due to cardiomyopathy.

STATISTICS

The SF and Massl were compared between the groups, before and after treatment by repeated measures ANOVA and Student's t-tests. Variables of chest irradiation and mean doses/m^2 of AD, CY and AC, were analysed by Fisher's exact probability test and unpaired t-tests, with Bonferroni correction.

Analysis for SF in relation to age at diagnosis, sex, type of tumour, radiation to the chest, doses of AD, CY, and AC and DC of AD was undertaken using linear regression for each group separately and following comparison of each slope by covariance analysis, the groups were pooled and linear regression performed.

TABLE IV. Effects of Chemotherapy, Irradiation and Gender on SF Pre- and Postchemotherapy

	Pre		Post		
	m	S.D.	m	S.D.	*P*
ES[a]	0.34	0.03	0.25	0.07	<<0.001
STS[d]	0.36	0.05	0.30	0.05	<0.0004
	P = NS.			*P* = 0.0097	

Postchemo SF% According to Severity

SF[c]	<0.2	0.2–0.27	>0.27
ES	6 (M:2; F:4)[b]	7 (M:5; F:2)	17 (M:10; F:7)
STS	1 (F)	8 (M:5; F:3)	17 (M:11; F:6)

Comparison of SF in Males and Females

	Pre-SF		Post-SF	
	Male	Female	Male	Female
m	0.35	0.35	0.29	0.26
S.D.	0.04	0.04	0.05	0.08
n	33	23	33	23

Effect of Irradiation on Shortening Fraction

	No XRT[e]	XRT	Total
SF < 0.2	5/45 (11%)	2/11 (18%)	7/56 (12.5%)
		P = 0.87	

[a]ES, Ewing sarcoma.
[b]F, female, M, male.
[c]SF, shortening fraction.
[d]STS, soft tissue sarcoma.
[e]XRT, irradiation.

RESULTS

Clinical Outcome

Table I shows the clinical data. Patients with STS were significantly younger ($P = < 0.001$). Six of ES (male: 2; female 4) patients developed clinical cardiomyopathy needing anti-failure treatment. Two of these patients died with AD cardiomyopathy which was confirmed at autopsy; one patient received a cardiac transplant. An additional ES patient required pacemaker insertion for sick sinus syndrome. None of the STS were in congestive failure.

Echocardiographic Outcome

Table IV shows the SF pre- and postchemotherapy for both groups. The baseline SF was within normal limits for each group. Mean postchemotherapy SF fell significantly in both groups ($P \ll 0.001$ and $P = 0.0004$, respectively), but was worse in ES vs. STS ($P = 0.0097$). Six of the ES patients in cardiac failure had postchemotherapy SF < 0.20, whereas only one of the STS patients had a SF < 0.20 ($P = 0.03$). An additional six ES patients (male: 5; female: 1) and nine STS (male: 7; female: 2) patients had SF between 0.20 and 0.27. None of these 15 patients were symptomatic. There was no difference in the SF of males compared to females.

With Bonferroni correction there was no significant difference in mean AD, CY and AC doses (Table III). The doses of AD were similar for patients with SF < 0.20 or >0.20. The DC for AD was higher for ES than STS ($P = 0.001$). Regression analysis of SF vs. DC showed a trend for decreasing SF with increasing DC. The slopes of SF vs. DC for each group were not different; for ES SF = −.0005DC + .296, R = −.1904, $P = .3136$, for STS, SF = −.0007DC + .317, R = −.2744, $P = .2287$. For the combined STS and ES groups, SF = −.0007DC + .314, R = .3338, $P = .0167$. Massl for ES pretherapy 95 ± 22 was not different than post 101 ± 29 g/m^2 and STS pre 82 ± 18 vs. post 78 ± 19.

Two of 11 patients with chest irradiation (1 of 8 ES; 1 of 3 STS) had an SF < 0.2 compared to five out of 45 patients without chest irradiation (Table IV). Mean SF for combined ES and STS with and without radiation were also similar. It is noteworthy that one patient who developed cardiomyopathy at a relatively low total accumulated dose of AD did receive chest irradiation.

The characteristics of the seven patients with SF < 0.2 are outlined in Table V. Six of the seven patients had ES.

DISCUSSION

Several factors have been reported to increase the role of AD-induced cardiomyopathy. These are the size of the individual dose [22,23] the total cummulative dose [3–8], concurrent administration of CY [13–16,24] nutritional status [25], irradiation to the chest [9–12], younger age, [17] and sex [26]. In our review, none of these factors except for age were shown to correlate with an increased incidence of cardiomyopathy although nutritional status was not evaluated.

In our review, there was a statistically significant increased risk of cardiomyopathy in patients with ES compared with patients with STS. As the mean doses were not different, the most likely explanation for this is the difference in scheduling of AD. We demonstrated a statistically significant increase in the risk of toxicity associated with the combination of high individual dose and shorter interval between AD doses as measured by the DC. Pratt et al. [27] and Lipshultz et al. [17] found that young children are more likely to experience cardiotoxicity. In our study, the mean age for the ES group was significantly higher than the STS group, which is the opposite of the expected effect and may emphasise the increased risk of the therapeutic regimen.

Cardiotoxicity is thought, in part, to be related to the serum concentration of AD. Since the frequency of administration of AD was greater in ES patients than in STS patients and the individual doses of AD were also different, we evaluated the effect of dose concentration on the incidence of cardiomyopathy. The formula used included the size of the individual dose as a variable, and

TABLE V. Details of Patients With SF < 0.20

Patients	Age at diagnosis (yrs)	Type of tumour	Chemotherapy g/M2	Irradiation	Last SF[e]	Outcome
1 M[d]	9.73	ES[c]	AD:0.303[a] CY:10.5[b]	RT 9TH RIB	0.15	alive
2 M	15.09	ES	AD:0.428	none	0.19	alive
3 F[d]	3.35	ES	AD:0.350 CY:16.89	none	0.19	alive
4 F	2.15	ES	AD:0.340 CY:7.3	L-1	0.16	died: cardiac
5 F	10.51	ES	AD:0.450 CY:16.8	none	0.04	alive transplant
6 F	13.25	ES	AD:0.375 CY:15.00	none	0.07	alive
7 F	1.93	STS[f]	AD:0.400 CY:5.5	none	0.16	died: disease

[a]AD, adriamycin.
[b]CY, cyclophosphamide.
[c]ES, Ewing sarcoma.
[d]F, female; M, male.
[e]SF, shortening fraction.
[f]STS, soft tissue sarcoma.
Rt = right.
L1 = first lumbar vertebrae.

regression analysis suggested a trend for decreasing SF with DC. There are other published formulae for calculating "dose intensity" which differ in their method of calculating the time periods between doses, but a standard proven optimal formula has not yet been developed [28,29]. Many oncologists are advocating infusion of AD to reduce peak serum levels and reduce cardiotoxicity. At the same time, there is an effort to improve cure rates by increasing chemotherapeutic, dose intensity. It is therefore important to further evaluate the relative roles of the size of the individual dose and frequency of administration of adriamycin on cardiotoxicity.

The Pediatric Oncology Group and the Children's Cancer Group have recently completed a study in patients with ES in which AD was given at 75 mg/m^2 once per three or six weeks [30]. This should offer an opportunity to obtain a definite answer to the relative importance of the size of the individual dose and frequency of administration in the etiology of AD cardiotoxicity.

This study implicated DC as a possible factor in the pathogenesis of cardiotoxicity in ES. Other unidentified factors may exist to explain our findings. The finding that Ewing tumours have a specific chromosomal abnormality [31] is of interest and of further speculation is that this may have a biological role. Further prospective studies may clarify which factors are significant in the etiology of cardiomyopathy.

ACKNOWLEDGMENTS

The authors thank Eustace S. de Souza, Beverley Johnston, and Terri Potts for performing echocardiography.

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